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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,895	10/23/2003	Hans-Joerg Moebius	MERZ 36	9019

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THE FIRM OF HUESCHEN AND SAGE
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EXAMINER	
OLSON, ERIC	
ART UNIT	**PAPER NUMBER**
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/691,895	MOEBIUS, HANS-JOERG	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-74* is/are pending in the application.

4a) Of the above claim(s) *37-55 and 62-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-61 and 66-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *January 22, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application claims priority to provisional application 60/691895, filed October 24, 2002. Applicant's preliminary amendment submitted February 14, 2005 is acknowledged wherein claims 1-36 are cancelled and new claims 37-74 are introduced.

Election/Restrictions

Applicant's election without traverse of group IV, drawn to a pharmaceutical composition comprising a nonbridged aminocyclohexane derivative, filed January 22, 2007, is acknowledged.

Claims 37-55 and 62-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on January 22, 2007.

Claims 56-61 and 66-74 are pending in this application and examined on the merits herein.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Te claimed invention is directed to non-statutory subject matter. Claim 56 provides for the use of a combination of a 1-aminocyclohexane derivative and an acetylcholinesterase inhibitor, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 56 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56-61, 66, and 70-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 56-61 and 70-74 refer to aminocyclohexane **derivatives**. It is not clear from the language of the claims or from the specification what compounds are considered to be derivatives of aminocyclohexane. This term has a number of meanings in the art, referring to various possible substitutions and reaction products related to a parent compound. There is no

one single agreed-upon definition of what a derivative is. Similarly, claim 66 refers to substituted compounds without defining what substituents are to be attached to the compound. For these reasons, the instant claims are indefinite.

Claims 56-60 and 66-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions for treating specific dementias such as Alzheimer's disease, does not reasonably provide enablement for compositions for treating all dementias associated with a CNS disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a pharmaceutical composition. While the intended use of a composition does not materially affect its structure or other

physical, chemical, or biological properties, a composition claim reciting an intended use must enable one skilled in the art to practice the intended use.

The state of the prior art: Certain 1-aminocyclohexane derivatives are known in the prior art to be NMDA receptor antagonists with efficacy against Alzheimer's disease. Acetylcholinesterase inhibitors are also widely known to be useful for this purpose. However, the prior art does not teach that these compounds, alone or in combination, are universally applicable to all dementias associated with a CNS disorder.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: According to the Merck Manual of Diagnosis and Therapy, (reference included with PTO-892) dementia can be caused by a number of different causes. Many of these, such as Alzheimer's disease, Amyotrophic lateral sclerosis, brain trauma, brain tumors, Huntington's disease, Parkinson's disease, prion disease, and infectious diseases of the central nervous system, are considered to be central nervous system disorders. (p. 1393, table 171-4) Dementia is a symptom which can result form many different causes, rather than a specific disorder that can be treated by targeting one particular biological target. While treating the underlying disease can affect the progression of dementia, there is no therapeutic agent capable of treating all CNS disorders that can result in dementia. For example, therapeutic agents for treating brain tumors are ineffective against Alzheimer's disease, and vise versa. There is no evidence that cholinergic-enhancing drugs (such as acetylcholinesterase inhibitors) are of any benefit in disorders other than Alzheimer's disease. (p. 1395, right column, first paragraph)

The Breadth of the claims: The claimed invention includes compositions for the treatment of any CNS disorder causing dementia, regardless of the cause of the disorder.

The amount of direction or guidance presented: The instant specification provides evidence that he claimed compositions are effective in the treatment of Alzheimer's disease, but does not provide such evidence for dementias generally. In fact, the mechanism by which the compounds are disclosed to work (acetylcholinesterase and NMDA receptors) is expected to be specific to Alzheimer's disease.

The presence or absence of working examples: The working examples provided all concern the treatment of Alzheimer's disease and do not indicate any activity of the claimed compositions for the treatment of other disorders.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the generic treatment of dementia. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would have to determine which dementias other than Alzheimer's disease can be successfully treated using the claimed composition. Doing so would require repeated experimentation on suitable models of a wide range of unrelated conditions, ranging from Parkinson's disease to HIV infection to brain cancer, none of which are known in the art to be treatable in any way with acetylcholinesterase inhibitors and NMDA receptor antagonists. The experimentation would likely involve

diverse animal models of various diseases, as dementia is a symptom that cannot be measured *in vivo*, such as in a tissue culture or receptor binding assay. Animal experimentation carries a particular burden due to the complications of maintaining and working with live animals and the ethical requirements associated with such research. Because the prior art, and Applicant's specification, provide no reasons to believe that the claimed compositions are useful beyond the well-known utility against Alzheimer's disease, the experimentation would be undertaken with no expectation of success. Therefore the experimental burden is deemed to be undue and unpredictable.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of dementias other than Alzheimer's disease.

Claims 56-61 and 66-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compositions comprising the specific acetylcholinesterase inhibitors and aminocyclohexane derivatives disclosed in the specification, does not reasonably provide enablement for a combination of any acetylcholinesterase inhibitor and any aminocyclohexane derivative. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The instant claims involve a pharmaceutical composition comprising two components. In order to meet the enablement requirement, one skilled in the art would need to be able to produce a pharmaceutically useful composition by combining any of the claimed ACHE inhibitors with any of the claimed aminocyclohexane derivatives, or at least to easily determine which embodiments are or are not functional.

The state of the prior art: Acetylcholinesterase inhibitors and NMDA antagonists are known in the prior art to be useful for the treatment of Alzheimer's disease. However, the full scope of all possible acetylcholinesterase inhibitors is not known. Neither is it known which of the billions of possible aminocyclohexane derivatives are NMDA antagonists.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The field of drug-drug interactions is unpredictable, and interactions between two broad classes of drugs cannot be predicted based on a single example. Avery's Drug Therapy, 3rd edition, states that, "Pharmacokinetic interactions observed *in vitro* or in animals will not necessarily occur in man," "Interactions will not necessarily occur in all patients receiving a given combination of drugs known to have a potential for interaction in man," and "Many clinically important interactions, especially those of a pharmacokinetic nature, depend on a variety of factors additional to the drugs given." (Chapter VIII, p. 255, Synopsis of Important Principles, no. 4-6) Although the cited text deals primarily with adverse drug-drug interactions, beneficial drug-drug interactions function in a similar manner according to similar mechanisms. Thus the determination of every possible interaction between two broad classes of drugs is expected to be highly unpredictable.

Furthermore, the biological properties of novel bioactive compounds are highly unpredictable. While compounds having similar structure are expected to function similarly, the scope of the claimed compositions includes many compounds having no structural similarity to any known drugs. Therefore the pharmaceutical activities of the claimed compositions is highly unpredictable.

Finally, the art of organic synthesis is also unpredictable in that a nontrivial amount of experimentation is necessary to arrive at a synthetic method for producing a reasonably complex compound. Because the claimed invention includes many totally novel compounds, complex synthetic schemes would have to be developed in order to obtain all of these compounds.

The Breadth of the claims: The instant claims are very broad, including a wide variety of compounds of differing structures, as well as differing physical, chemical, and pharmacological properties united solely by the presence of a single biological activity, in the case of acetylcholinesterase inhibitor, and by the presence of a cyclohexyl functionality and an amino functionality connected by a reasonably small linker in the case of aminocyclohexane derivatives. Although some of the claims define a single ACHE inhibitor or aminocyclohexane derivative, all claims are generic to at least one member of the combination.

The amount of direction or guidance presented: A number of compounds are recited which are useful in the claimed invention. Combinations between these compounds are considered to be preferred embodiments of the invention. Experimental protocols are given which could be used for the measurement of therapeutic efficacy. However, no guidance is given that would allow one skilled in the art to discover novel ACHE inhibitors or aminocyclohexane NMDA receptor antagonists

The presence or absence of working examples:

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable art such as the prediction of drug-drug interactions. See MPEP 2164.

The quantity of experimentation necessary: According to the 2006 Chemical Abstracts catalog, (Reference Included with PTO-892) the Chemical Abstracts Registry contains entries for more than 26 million organic and inorganic substances. The number of these substances which are known definitively either to be or not to be useful

in the claimed invention is dwarfed by the number for which their utility not known. The existing literature does not identify any general method by which these classes of compounds can be identified across all classes of molecular entities claimed other than by synthesizing and testing each one. In order to practice the invention with the full range of chemical compositions beyond the limited number disclosed in the specification, one skilled in the art would be required to undertake a full-scale, high-throughput drug discovery program to discover the additional ACHE inhibitors and NMDA receptor antagonists not specifically recited in the specification. In fact, one skilled in the art would also be forced to retest many of those molecules specifically identified in the specification, as no specific IC50 values or other therapeutic properties are given by which one skilled in the art could determine which of the recited compounds are the best drug candidates. Note that as the specification does not limit the scope of the invention to combinations comprising only organic small molecule ACHE inhibitors, the compounds used in the claimed invention could comprise oligonucleotides, polysaccharides, proteins, inorganic compounds, or any other substances that inhibit acetylcholinesterase.

In the process of screening the extensive number of compounds required to practice the claimed invention, one skilled in the art would be forced to synthesize said molecules. As no synthetic procedures are described and no references cited that teach synthetic protocols to synthesize known or potential acetylcholinesterase and aminocyclohexane derivatives, other than the admittedly incomplete list of examples, one skilled in the art wishing to practice the invention would be forced to design novel

synthetic pathways. Since synthesis of organic small molecules is complex, the entire scope of claimed molecules cannot be synthesized by simple variations on a core synthetic scheme. Since no structural limitations are given to the claimed invention, the list of compounds to be synthesized would include an enormously diverse set of structures and require an equally diverse array of synthetic procedures to produce them. Thus one of skill in the art would be forced to invest a considerable amount of time and effort devising chemical syntheses spanning all fields of organic, inorganic, and biological chemistry.

In addition to synthesizing candidate compounds and carrying out *in vitro* studies on the molecular target, one skilled in the art wishing to practice the invention using every possible synergistic combination would also be required to undertake *in vivo* tests in animal models of relevant conditions, such as the ones disclosed in the specification. Because many different types of synergism are included within the breadth of the claims, multiple experiments would be necessary. At the very minimum, synergistic effects for the treatment of pain, seizures, depression, cartilage damage, and proliferative disorders would have to be screened for, along with possible negative side effects arising from drug-drug interactions. Animal experiments include, along with the actual induction of disease state, administration of the potential pharmaceutical compound, and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, and disposal of dead animals after the protocol is finished. Human tests involve a similar or greater burden, particularly in recruiting subjects and complying with

regulatory and ethical requirements. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated thousands of times, and involve the maintenance, killing, and disposal of at tens of thousands of experimental animals at minimum, to establish the suitability or lack thereof for each compound found to possess the desired activity *in vitro*.
The sort of industrial-scale interdisciplinary drug discovery program described in the preceding paragraphs would present an undue amount of experimentation to require of anyone wishing to practice the invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims and the lack of guidance and working examples, Applicants fail to provide information sufficient to practice the claimed invention for any possible synergistic combination of an acetylcholinesterase inhibitor and an aminocyclohexane derivative.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 56-61 and 66-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. (US patent 6071966, cited in PTO-892) in view of Dooley et al. (Reference included with PTO-892) Gold et al. discloses a pharmaceutical composition comprising a compound having a structure identical to the aminocyclohexane derivatives of instant claims 66 and 67. (column 4, line 22 – column 6, line 5) For example, the compounds 1-amino-1,3,5-trimethylcyclohexane (neramexane), 1-amino-1,3,3,5-tetramethylcyclohexane, and 1-amino-1,3,3,5,5-pentamethylcyclohexane, are compounds of the claimed invention that are explicitly taught by Gold et al. Examples of pharmaceutical compositions of Gold et al. include tablets with 10 mg of active agent (column 21, lines 20-35) and an injectable solution with 12 mg of active agent. (column 22, lines 15-25) The compositions are disclosed to be useful for the treatment of neurodegenerative diseases including Alzheimer's disease. (column 36, lines 31-52) Gold et al. does not disclose a composition of this type further comprising an acetylcholinesterase inhibitor.

Dooley et al. discloses that Donepezil is a reversible acetylcholinesterase inhibitor that is indicated in the management of patients with mild to moderate Alzheimer's disease. (p. 206, left column, second paragraph) Gold et al. also discloses hat a dose of 5 or 10 mg of donepezil per day significantly improved cognition in patients with mild to moderate Alzheimer's disease. (p. 213, right column, second paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to add 5 or 10 mg of donepezil to the pharmaceutical compositions of Gold et al. One of ordinary skill in the art would have been motivated to modify the invention in this manner because the prior art discloses that donepezil and the compounds of Gold et al. are both useful for the same purpose, namely treating Alzheimer's disease. One of ordinary skill in the art would reasonably have expected success because both compounds are known in the prior art to be effective individually for this purpose. It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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